DNA Structure and Dynamics II

1967-Pos Board B104
Targeting Human Telomeric G-Quadruplex DNA by Berberine Analogs: A Comparative Biophysical Investigation
Debipreeta Bhowmik[1], Gopinatha Suresh Kumar[2].
[1]Chemistry, Indian Institute of Chemical Biology, Kolkata, India,
[2]Chemistry, Indian Institute of Chemical Biology, Kolkata, India.
Nucleic acids are potential target molecules in various anticancer therapies. Understanding how drug molecules interact with nucleic acid has become an active research area at the interface between chemistry, molecular biology and medicine. Berberine is the most widely known alkaloid belonging to the protoberberine group, exhibiting myriad therapeutic applications. The anticancer potency of berberine is thought to emanate from its strong interaction with nucleic acids, and inhibition of the enzymes topoisomerases, telomerases. Berberine also binds strongly to the G-quadruplex structure, an alternative DNA structural motif. The capability of berberine analogs bearing substitution at 9 and 13-position to strongly bind G-quadruplex structure is studied for developing effective anti cancer therapeutics. Compared with berberine, these derivatives exhibit stronger binding affinity with G-quadruplex and the non cooperative binding affinity of berberine was propagated in the analogs also. The circular dichroism studies indicated that the alkaloid bound quadruplex DNA has a fold similar to the unbound form. In all cases, the stoichiometry was found to be one mole of ligand binding per mole of quadruplex. Calorimetric results indicated that the interaction of these analogs with the quadruplex was entropy driven phenomenon. The negative heat capacity changes in all systems along with significant enthalpy-entropy compensation may be correlated to the involvement of multiple weak non-covalent forces in the complexation process. The amino alkyl substitution at 9-position were found to be more effective in stabilizing G-quadruplex structure compared to the phenyl alkyl substitution at 13-position. Detailed studies on these analogs stabilizing telomeric G-quadruplex-DNA through entropy driven process with high binding affinity shall be presented that enable consideration as a leads compounds for telomerase inhibition and anticancer therapy.

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Studying Ligand Binding and Site-Specific Mode of DNA Binding by Gamma-Butyrolactone Receptor Protein CprB from Streptomyces Coelicolor A3(2) using Two Different Fluorescence Techniques
Anwesha Biswas[1], G. Naresh Patwari[1], G. Krishnamoorthy[2], Ruchi Anand[1].
[1]Department of Chemistry, Indian Institute of Technology Bombay, Mumbai, India, [2]Department of Chemical Sciences, Tata Institute of Fundamental Research, Mumbai, India.
Quorum sensing is a cell density dependent phenomenon that utilizes inducers like γ-butyrolactones (GBLs) and their receptor proteins in *Streptomyces* species to control expression of a plethora of genes initiating antibiotic production and other secondary metabolic pathways. The receptor proteins regulate by binding to the DNA in the promoter regions of genes; release from the DNA takes place on binding to their specific GBL molecules, initiating the expression of the downstream genes.
Several cognate GBLs binding to the GBL receptor family of proteins remain elusive. Here, using the only structurally characterised member of this family, CprB from *Streptomycescoelicolor* A3(2) as a model system, we suggest tryptophan quenching as a method for ligand screening, for the family. The intrinsic fluorophore tryptophan (W127) is a conserved residue in the family residing within the ligand binding pocket of CprB. Docking studies show interaction of GBLs with W127 and has been identified as the cause of fluorescence quenching observed on administration of two chemically synthesized GBLs (http://dx.doi.org/10.1021/jp503589h)
CprB is also known to specifically bind various promoter sequences. Though structural breakthrough has been achieved for the complex with a consensus sequence, there is dearth of information on the mode of binding to the others. To delineate the same, motional dynamics of 2-aminopurine (2-AP) has been monitored after its incorporation at different positions within the consensus sequence and a biologically relevant cognate sequence. Comparing the dynamics restriction of 2-AP across the two sequences has helped reveal a signature pattern of DNA binding by CprB. The study highlights how the technique can be a powerful tool to understand the mode of binding even in the absence of structural breakthrough (Manuscript under review).

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DNA Pseudoknots with Appropriate Loop Lengths and Sequence Complementary to the Stem form Stabilizing Base-Triplet Stacks
Calliste Reiling, Irine Khutsishvili, Luis A. Marky.
University of Nebraska Medical Center, Omaha, NE, USA.
Pseudoknots have been found to play important roles in RNA function, such as the critical roles in altering gene expression by inducing ribosomal frameshifting in many viruses and in the 5' UTR of mRNA as riboswitches. We used a combination of UV spectroscopy and differential scanning calorimetry to investigate the unfolding of DNA pseudoknots that mimic the formation of a local triplet helix found with RNA pseudokkots, explaining −1 ribosomal frameshifting. Specifically, we determined the unfolding thermodynamics for the following DNA set of pseudoknots with sequence: d(TCTCTT_nAAAAAAAA GAGAT_5TTTTTTT), where the length of the "T_n" loop was varied from n = 5, 7, 9, and 11. The increase in loop length yielded higher T_{Ms}, 53C to 59C, and folding enthalpies ranging from −60 kcal/mol to −105 kcal/mol, resulting in a significant stabilization of the pseudoknots, G = −8.5 kcal/mol to −15.9 kcal/mol. We also varied the length of the loop for two sets of control molecules: straight hairpin loops and pseudoknots in which the 5' loop is not complementary to the stem. Their increased loop length yielded slight changes in both the T_{Ms} and folding enthalpies, consistent with a slight decrease in stability with the straight hairpin loops and a slight increase in stability with the pseudoknots. Therefore, the increase in enthalpy, ~14 kcal/mol per step of two loop thymines, is explained in terms of the formation of a single base-triplet stack. For instance, the pseudoknot with the loop of 9 thymines forms two base-triplet stacks. Supported by Grant MCB-1122029 from NSF and GAANN grant P200A120231 from the U.S. Department of Education.

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Sequence Dependent Plectoneme Dynamics
Marco Tompitak[1], Behrouz Eslami Mossallam[1], Gerard Barkema[2], Helmut Schiessel[1].
[1]Instituut-Lorentz, Leiden University, Leiden, Netherlands, [2]ITF, Utrecht University, Utrecht, Netherlands.
In recent years, both theoretical and experimental indicators have been gathering, showing that sequence effects on the physical properties of DNA molecules contribute nontrivially to the molecule's behavior. Here we present the first results of a study of sequence effects on the formation and dynamics of plectonemes, the supercoiled structures produced when the DNA is put under torsional stress. Using, for the first time in this context, a fully sequence-dependent, non-coursegrained rigid base pair model for the DNA molecule, we examined the process of sliding a formed plectoneme along a DNA molecule in its entirety as a mechanism for plectoneme transport. We were able to map out the relevant energy landscapes and we find that we can rule out sliding as the dominant transporation mechanism.

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Mismatched DNA Base Pairs Show Increased Conformational Fluctuations
Adelaide Kingsland, Lutz Maibaum.
Chemistry, University of Washington, Seattle, WA, USA.
Base pair mismatches in DNA can have many adverse consequences, yet the exact mechanism by which mismatches are repaired is unknown. Both matched and mismatched DNA sequences were studied using molecular dynamics in biased and unbiased simulation. Significant differences were found between matched and mismatched pairs in structure, hydrogen bonding, and base flip work profiles. Mismatched pairs show greater movement perpendicular to the DNA strand and a lower free energy barrier for base flip than matched pairs. This supports experimental findings that the primary mechanism utilized by mismatch repair enzymes is to fully flip the base into the active site.

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The Study of Complexation Process between Cationic Gemini Surfactants and DNA using Structural and Spectroscopic Methods
Weronika J. Andrzejewska[1], Michalina Skupin[1], Magdalena Murawska[1], Andrzej Skrzypczak[2], Maciej Kozak[1].
[1]Macromolecular Physics, Adam Mickiewicz University in Poznan, Poland, Poznan, Poland, [2]Faculty of Chemical Technology, Poznan University of Technology, Poland, Poznan, Poland.
Dicationic (gemini) surfactants are intensively studied group of chemical compounds, because of the broad range of applications in medicine, chemical technology or pharmaceutical industry. In solution they can form with nucleic acids the complex structures (lipoplexes), which can be used as drug delivery systems